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ORIGINAL PAPER

Invasive pulmonary aspergillosis in patients with COPD: a report of five cases and systematic review of the literature

P Samarakoon and AO Soubani
Division of Pulmonary, Allergy, Critical Care and Sleep, Wayne State University School of Medicine, Harper University Hospital, Detroit, MI, USA

Background: There are increasing reports describing invasive pulmonary aspergillosis (IPA) in patients with chronic obstructive pulmonary disease (COPD) without the classic risk factors for this severe infection. The available literature on this association is based on case reports or small case series. The aim of this review is to systematically review these cases and describe the clinical features, diagnostic studies and outcome.
Methods: We identified all the cases of IPA and COPD reported in the literature and had enough clinical information. We also included five cases of IPA in patients with COPD identified by the authors. These cases were systematically reviewed for clinical features, diagnostic studies and outcome.
Results: There were 60 cases of IPA in patients with COPD identified from the literature. The total number of cases reviewed was 65. The mean age was 65.1 years, the mean FEV1 was 39% of predicted (n = 17, range 19–56%). Forty-nine patients were documented to be on systemic corticosteroids. The mean dose was 24 mg/day (range 15–65 mg/day). Five patients were only on inhaled corticosteroids and in 11 patients there was no documentation of corticosteroid therapy. The clinical and radiological findings were nonspecific. Thirteen patients had documented evidence of disseminated IPA. Sputum examination was positive for *Aspergillus* in 76% and bronchoscopy with bronchoalveolar lavage that was positive in 70%. The diagnosis of IPA was definite in 43 patients and probable in 22 patients. Forty-six patients were treated with anti-fungal therapy. Fifty-nine patients (91%) died with IPA.
Conclusion: Invasive pulmonary aspergillosis is an emerging serious infection in patients with COPD. The majority of these patients have advanced COPD and/or on corticosteroid therapy. The clinical and radiological presentation is nonspecific. High index of suspicion is necessary for the timely treatment of these patients. *Chronic Respiratory Disease* 2008; **5**: 19–27

Key words: aspergillosis; COPD; outcome; pulmonary fungal infections

Aspergillus spp. are ubiquitous fungi acquired by inhalation of airborne spores and may cause life-threatening infections especially in immunocompromised hosts. *Aspergillus* spp. are commonly isolated from the soil, plant debris and the indoor environment, including hospitals. *Aspergillus*, mainly *A. fumigatus*, causes a variety of clinical syndromes that range from invasive pulmonary aspergillosis (IPA), which is a severe disease and a major cause of mortality in severely immunocompromised patients to chronic necrotizing aspergillosis, which is locally invasive disease that is seen mainly in patients who are mildly immunocompromised or have chronic lung disease. Aspergilloma and allergic bronchopulmonary aspergillosis (ABPA) are two noninvasive pulmonary diseases caused by *Aspergillus*. Aspergilloma is a fungus ball that develops in a pre-existing lung cavity, whereas ABPA is a hypersensitivity disease of the lungs that almost always affects patients with asthma or cystic fibrosis.

Invasive pulmonary aspergillosis was first described in 1953.[1] The incidence of IPA has increased during the past two decades due to widespread use of chemotherapy and immunosuppressive agents. Groll *et al.*, documented that the rate of invasive mycoses increased from 0.4 to 3.1% of all autopsies performed between 1978 and 1992.[2] In addition, invasive aspergillosis increased from 17% of all mycoses found on autopsy at the beginning of the study to 60% at the end of the 14-year study period. This serious infection was primarily described in severely immunocompromised patients such as those with prolonged neutropenia, hematological malignancy, on prolonged high dose corticosteroid therapy and hematopoietic stem cell and solid organ transplantation

Correspondence: Ayman O Soubani, MD, Associate Professor of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep, Wayne State University School of Medicine, Harper University Hospital, 3990 John R-3 Hudson, Detroit, MI 48201, USA.
Email: asoubani@med.wayne.edu

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recipients.[3] However, there are more and more reports of IPA in patients without the classic risk factors. These reports include patients with chronic obstructive pulmonary disease (COPD) and the critically ill patients.[4–9] In patients with COPD, the description of IPA is based on case reports or small case series. This review aims at systemically describing the clinical features, diagnostic methods and treatment and outcome of cases of IPA in patients with COPD described in the literature.

Methods

We put forward an outline for our review that will systematically document the following variables: demographics, underlying illnesses, clinical presentation, radiological findings, diagnostic studies, treatment and outcome. We searched the Pubmed/Medline database until June 2006 for articles published in the English Language literature using the keywords or text words aspergillosis or IPA cross-referenced with chronic obstructive airway disease. Where applicable, we reviewed references cited in these articles. We included in our review all the cases that had enough information to fulfill most of the above variables. We also included five patients found at our institution or the authors have been consulted on. We excluded all cases that did not have details about the illness, or had other known risk factors for IPA such as neutropenia, hematological malignancy or hematopoietic stem cell transplantation or solid organ transplantation. Care was taken to ensure that the same patient was not included twice in our analysis, as some patients were described more than once in the literature. The diagnosis of COPD was based on that made by the original reports. The diagnosis of IPA was reconciled with the criteria suggested by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EROTIC/MSG).[10] We considered the patient to have 'definite' IPA when there was histopatholoigcal demonstration of the *Aspergillus hyphae* in a tissue sample or positive culture from a sterile site with clinical evidence of infection. The patient was considered to have 'Probable' IPA when *Aspergillus* was isolated by culture or cytological smear from lower respiratory tract specimen such as sputum, tracheal secretions or bronchoalveolar lavage (BAL) associated with compatible clinical and radiological findings – as described by the EROTIC/MSG criteria. Patients with the diagnosis of possible IPA were not considered for this analysis.

Results

There were 60 patients in the literature,[6,11–29] and five new cases identified by the authors that met our criteria for IPA and COPD (Table 1) leading to a total of 65 cases.

Table 1 Summary of five new patients described by the authors

Age	*43*	*63*	*76*	*49*	*62*
Sex	M	M	M	M	M
Race	AA	AA	W	W	W
Underlying illnesses	COPD, recurrent pneumonia	COPD	COPD, lung cancer (s/p lobectomy two years earlier)	COPD, IV drug use	COPD, Dressler's syndrome
Corticosteroid therapy	None	None	None	Hydrocortisone 200 mg/day for adrenal insufficiency	Prednisone 50 mg/day
Admitting diagnosis	Acute COPD exacerbation	Pneumonia	Pmeumonia, empyema	Pneumonia	Pneumonia
CT findings	CT head: two ring enhancing lesions	Multiple cavitary pulmonary nodules	Right pulmonary infiltrates and pleural effusion	RUL cavitary lesion, bilateral pulmonary infiltrates	LUL infiltrate
WBC	10 600	24 400	24 000	19 000	18 900
Other organisms isolated	None	*Candida, klebsiella*	Pseudomonas	None	None
Diagnostic method	Brain biopsy: *A. flavus*	blood culture: *A. niger*	Pleural fluid: *A. fumigatus*	Sputum: *A. niger* BAL: *A. niger* Serum galactomannan: 0.74	Bronchoscopy with bronchial biopsy: *A. niger*. Autopsy: disseminated aspergillosis
Diagnosis	Definite IPA	Definite IPA	Definite IPA	Probable IPA	Definite IPA
Treatment	Amphoteirin lipid formulation	No anti-fungal treatment	Amphotericin B, imipenem	Voriconazole	Amphotericin lipid formulation
Outcome	Expired after 21 days due to multiorgan system failure	Expired after 12 days due to respiratory failure	Survived	Expired after six days due to multiorgan system failure	Expired after eight days due to multiorgan system failure

Baseline clinical characteristics

There were 52 males and 13 females, for a male to female ratio of 4:1. The mean age was 65.1 year (range 45–83 years) . The race was often not recorded in the literature, however was available on 12 patients (eight whites and four blacks). All patients were diagnosed to have COPD. The duration of smoking was reported in 27 patients, with mean duration of 59 pack.years (range 20–120 pack.year). Six patients were described as having severe COPD and one patient as very severe COPD. Spirometry results were reported in 17 cases. The mean FEV1 was 1.18 L (range 0.75–2.15 L) and the mean FEV1% of predicted was 39% (range 19–56%). Twenty-two patients (34%) had a documented recent acute exacerbation of COPD 1–16 weeks prior to the diagnosis of IPA.

Forty-nine patients (75%) were on chronic systemic corticosteroids therapy prior to the diagnosis of IPA. Five patients (8%) were only on inhaled corticosteroids and in 11 patients details on the corticosteroids therapy were not documented. The mean corticosteroid dose was 24 mg/day (range 15–65 mg/day). The duration of corticosteroid therapy was documented in only 15 patients. In these patients, the median duration of therapy was 2.6 years (range 3 weeks–10 year). The dose of systemic corticosteroids was increased in 22 patients (34%) following hospitalization and prior to the diagnosis of IPA (Table 2).

Twenty-three patients (43%) had documented other comorbid illnesses. Atypical mycobacteria was present in three patients, two of them were due to *M. kansasii*. A remote history of *M. tuberculosis* was reported in three patients and all were previously treated. Other comorbid illnesses included polymyalgia rheumatica, asthma, cirrhosis, diabetes mellitus, pneumoconiosis, Dressler's syndrome after open heart surgery and lung cancer. Finally, 42 patients (65%) had no reported comorbid illnesses other than COPD.

Table 2 Baseline characteristics of COPD patients with IPA ($n = 65$)

Characteristics	*Data*
Age (mean, range)	65.1 years (45–83)
Sex (male/female)	52/13 patients
Smoking history (mean, range, n = 27)	59 pack.year (20–120)
FEV1 (mean, range, n = 17)	39% predicted (19–56%)
Recent acute exacerbation of COPD	22 patients
Comorbid illnesses	23 patients
Corticosteroid therapy	
Chronic treatment	49 patients
Dose of corticosteroids (mean, range)	24 mg/day (15–65)
Duration of therapy (mean, range)	2.6 years (3 weeks–10 years)
Recent increase in dose	22 patients
Only inhaled corticosteroids	5 patients
Corticosteroid therapy is not documented	11 patients

Clinical presentation

The clinical presentation was not consistently documented, however when mentioned, the presentation was nonspecific. Dyspnea was reported as the main symptom in 21 patients (32%). Cough was present in 17 patients (26%) and 10 (15%) had hemoptysis (three out of the 10 patients developed hemoptysis while in the hospital). Sputum production was mentioned in only eight patients (12%) and wheezing was reported in five patients (8%). Five patients (8%) had chest pain upon admission, out of whom two complained of right-sided pleuritic pain. Four patients (8%) had reported significant weight loss. Unusual initial presentations included three patients with backache who were found to have disseminated aspergillosis of the vertebral discs. The duration of symptoms was reported in 23 patients, with a median of 14 days (range 3–120 days). We arbitrarily defined onset as acute, if symptoms were present for 30 days or less before presentation and chronic, if present for more than 30 days. Most patients (20 patients) had acute onset, but few patients (three patients) had chronic symptoms.

The physical findings were also not consistently reported in the literature. Temperature was recorded in 11 patients (median 37.6°C, maximum 39.6°C). Crackles were reported in six patients, wheezing in five patients, bronchial breath sounds in four patients and pleuritic rub in one patient.

The main admitting diagnoses were acute respiratory failure in 27 patients (41%), acute exacerbation of COPD in 22 patients (34%), pneumonia in 13 patients (20%) and septic shock with multiorgan system failure in three patients (5%).

Radiological findings

The radiological evaluation was mainly based on chest radiographs. Twenty-three patients had computed tomography (CT) scan of the chest during their hospitalization. The chest radiograph on admission was reported as abnormal in 78% of patients, and no infiltrates in 22% of patients. The most commonly reported radiological abnormalities (based on chest radiograph and/or chest CT scan) were infiltrate or consolidation in 41 patients (63%); the infiltrates were bilateral in 10 of these patients. Cavitary lesions were reported in 10 patients (20%) and solitary or multiple nodules in four patients (6%). Pleural effusions were reported in three

patients (5%). The Halo sign was reported only in one patient. Mycetoma, lung mass, mediastinal lymphadenopathy and pleural thickening were reported each in one patient.

Diagnostic studies

Table 3 summarizes the diagnostic studies and their yield as reported in the literature. Sputum culture samples were positive in 76% of the cases in whom samples were submitted. Higher positive yield was seen when tracheal sections were tested (100% were positive). Bronchoscopy was performed on 44 patients (67%). In two patients, endobronchial lesions were described, and consisted of black friable, gritty material coating the bronchial tree. In both cases *A. niger* was isolated. Bronchoalveolar lavage was positive in 70% of those in whom the procedure was reported. Open lung biopsy was done in one patient. Other diagnostic studies included examination of the pleural fluid in two patients and both were positive. Computed tomography guided biopsy of vertebral discs was done in three cases and was positive for *Aspergillus* in two cases. Brain biopsy was done in one patient, and was positive for *Aspergillus* spp. Blood cultures were positive in two out of 22 patients (9%) in whom the results were documented (one with *A. niger* and the second for *A. flavus*).

Thirty patients underwent autopsy that confirmed the diagnosis of IPA. In 28 patients, there was evidence of *Aspergillus* infection antemortem. In 27 of these patients, *Aspergillus* was isolated from lower respiratory tract secretions (sputum, tracheal suction or bronchoscopy samples), and in one patient blood culture was positive for *A. flavus* and IPA was confirmed by postmortem examination. Autopsy was the only evidence of IPA in two patients.

Aspergillus antigen was positive in the cerebrospinal fluid analysis of one patient. Serum *Aspergillus* precipitin was elevated in two patients. *Aspergillus* polymerase chain reaction (PCR) was reported in two patients and was positive in one patient. Serum galactomannan test was positive in one patient. Other diagnostic studies included WBC (mean 17 400 cells/mm^3 and range 8400–41 000 cells/mm^3). Serum IgE level was elevated to 3400 IU/L in one patient. In one report of 15 patients with COPD and IPA, serum Lactate Dehydrogenase (LDH) was elevated in all patients.

The *Aspergillus* spp. was reported in 61 patients. The most common isolates were *A. fumigatus* in 51 patients (84%), *A. niger* in five patients (8%) and *A. flavus* in five patients (8%). Other microorganisms were isolated in 13 patients (20%). Of these five patients had *P aeruginosa*, four patients had *Candida* spp., two patients had *K pneumoniae*, two patients had *Legionella* and one patient had *Strongiloides stercoralis*.

On the basis of EROCTIC/MGS criteria, 43 patients (66%) had proven IPA and 22 patients (34%) had probable IPA. Table 4 summarized the primary diagnostic method in these cases.

Treatment and outcome

A total of 46 patients (71%) were treated with antifungal agents. Of these, 14 patients (30%) were treated with multiple agents. Amphotericin B was used in 43 patients, itraconazole in 10 patients, lipid amphotericin B formulation in three patients, 5-fluorocytosii (5FC) in two patients and voriconazole in one patient. Surgical interventions were reported in five patients (8%) and these included thoracotomy in one patient, chest tube drainage in two patients and laminectomy with decompression in two patients.

Fifty-nine patients (91%) died. All those who survived had proven IPA. The median time from the diagnosis of IPA and death was 18.3 days (range 2–112 days). Thirty-one patients (48%) were reported to have received mechanical ventilation and none of these patients survived. Thirteen patients (20%) had evidence of disseminated IPA, only two of these patients survived.

Table 3 Microbiological specimens submitted and recovered with *Aspergillus* spp

Specimen	*No. of patients*	*Positive for Aspergillus*
Sputum samples	34	26 (76%)
Tracheal aspirates	22	22 (100%)
Blood culture	22	2 (9%)
Bronchoalveolar lavage	23	16 (70%)
Transbronchial biopsies	6	6 (100%)
Bronchial washings	3	2 (66%)

Table 4 Main diagnostic method confirming IPA in COPD patients (n = 65)

Proven IPA (n = 43)	Transbronchial biopsy	6
	CNS (brain biopsy, CSF examination)	2
	Blood culture	2
	Vertebral body (CT guided biopsy, surgery)	2
	Open lung biopsy	1
	CT guided lung biopsy	1
	Pleural fluid analysis	1
	Autopsy	28
Probable IPA (n = 22)	Bronchoscopy (BAL, washing or brushing)	15
	Tracheal aspirate	4
	Sputum	3

The main causes of death were progressive respiratory failure in 53 patients (90%), septic shock in 25 patients (42%), renal failure in 19 patients (32%), massive hemoptysis in four patients (7%) and other causes that included intractable seizures, massive gastrointestinal bleeding, mesenteric necrosis and pancreatitis.

Comments

Invasive pulmonary aspergillosis is a serious infection that is mainly described in severely immunocompromised hosts. The classic risk factors for IPA include severe neutropenia, hematological malignancies such as leukemia, chronic high dose corticosteroids and hematopoietic stem cell transplantation (HSCT) and Solid organ transplantation.[3] Recently there are increasing reports that describe IPA in patients without the traditional risk factors. These reports include critically ill patients, postoperative patients and patients with COPD.

It is not clear why COPD patients may develop IPA (Table 5). An important risk factor is chronic corticosteroid therapy, usually for the treatment of underlying COPD. Most of the patients in this report (75%) have been on chronic systemic corticosteroids treatment. The daily dose of corticosteroids was usually moderate (mean of 24 mg/day) and in 34% of these patients there has been a recent increase in the dose of corticosteroids (usually for the treatment of acute exacerbation of COPD). Stuck *et al.*, reported that corticosteroids rarely lead to a serious infection in patients on doses equivalent to prednisone less than 10 mg/day or a cumulative dose less than 700 mg.[30] In a small number of patients (8%) the only documented corticosteroid therapy was inhaled corticosteroids. Corticosteroids increase the risk of IPA by affecting the function of macrophages and neutrophils, which are the two major immunoregulatory cells in the host defenses against *Aspergillus*.[31]

Another potential risk factor for IPA in COPD patients is the severe underlying lung disease. In this analysis, the severity of COPD was not reported in all reports; however several patients had low FEV1 or described to have severe or very severe COPD. It has been documented that chronic lung disease predisposes to colonization of airways by *Aspergillus* spp. and leads to other forms of *Aspergillus* related pulmonary disease such as aspergilloma and chronic semi-IPA.[29,32,33] It is possible that under certain circumstances, such as corticosteroid therapy, acute illness, antibiotics use or comorbid illnesses, this colonization changes to an invasive disease.

Furthermore, admission to parts of the hospital that are undergoing renovation or construction, which has been documented as a cause of outbreak of IPA in other patient populations, may be a factor in predisposing to IPA in patients with COPD.[34,35] The cases reviewed, did not mention whether any of the patients was admitted to parts of the hospital under construction. However, it may be warranted to avoid caring for COPD patients on corticosteroids in areas of the hospital undergoing renovation or construction. Frequent broad-antibiotics therapy, invasive procedures, mucosal lesions and impaired mucociliary clearance are known to predispose to fungal infections in general, and may be factors leading to IPA in hospitalized COPD patients.

Genetic factors may also play a role in the pathogenesis of chronic lung disease such as COPD and aspergillosis. There are experimental reports that show that pulmonary surfactant proteins (such as A and D) play a role in enhancing the phagocytosis and killing of *Aspergillus* by neutrophils and alveolar macrophages, and that deficiencies or abnormalities in these protein may play a role in the pathogenesis of IPA.[29,36,37] There are, at the same time, limited reports of abnormalities in these surfactant proteins in patients with emphysema.[38–40] So, it is possible that surfactant proteins deficiency or abnormalities play a role in the pathogenesis of IPA in patients with COPD. Furthermore, subtle immune defect (mannose-binding protein polymorphism) have been described in some patients with chronic pulmonary aspergillosis.[36,37] Interestingly, the genes encoding mannose-binding protein and surfactant are in close proximity on chromosome 10, which could imply linkage of defects. Further experiments are needed to verify the relation between these factors and the development of IPA in patients with COPD.

The majority of COPD patients with IPA had positive sputum and/or tracheal aspirates for *Aspergillus*. The major challenge to clinicians evaluating patients with positive lower respiratory tract samples for *Aspergillus* is to differentiate between colonization and IPA. Studies have shown that the significance of isolating *Aspergillus* spp. from lower respiratory tract samples is dependent on the host's underlying immune status. In immunocompromised patients,

Table 5 Potential risk factors predisposing COPD patients to IPA

Corticosteroid therapy
Severe underlying lung disease
Critical illness
Colonization of airways by *Aspergillus* spp.
Hospital construction or renovation
Impaired mucociliary clearance
Broad-spectrum antibiotics
Genetic factors (such as surfactant proteins or mannose-binding protein defects)

the isolation of *Aspergillus* is highly predictive of IPA, and may be adequate indication for anti-fungal therapy.[41–43] On the other hand, the majority of studies show that in immunocompetent patients, the isolation of *Aspergillus* is usually indicative of colonization and does not need further intervention. In a study of 66 elderly hospitalized patients with *Aspergillus* isolated from the sputum, 92% were consistent with colonization, and only 4.5% had IPA.[33,44] Similar observations were reported by others.[41,44] The current analysis, and other reports that increasingly document IPA in patients without the classic risk factors for invasive disease, suggest that isolation of *Aspergillus* spp. from the lower respiratory tract secretions should not be routinely dismissed as colonization, and these patients should be carefully evaluated to exclude IPA. On the other hand, negative lower respiratory tract cultures for *Aspergillus* do not exclude this diagnosis. Studies on IPA in immunocompromised patients showed that sputum cultures were negative in 70% of patients with proven IPA.[43] There is no consensus on how to further evaluate these patients, but we recommend closer observation, and considering further studies such as high resolution CT (HRCT) of the chest, serological studies to detect *Aspergillus* antigens, possible bronchoscopy, and in the critically ill patients, empirical anti-fungal therapy.

The radiological findings in this report were mainly based on chest radiograph, which is not sensitive or specific for the diagnosis of IPA. Several studies have shown that chest CT scan, especially with high resolution cuts is much more useful, and should be considered early if there is clinical suspicion of IPA.[45–47] The radiological findings of IPA in the COPD patients were mainly infiltrates or consolidations that have some predilection toward the upper lobes. Nodules with or without cavitations were documented in 36% of the cases. The classic halo sign, which is mainly seen in neutropenic patients early in the course of infection (usually in the first week), and appears as a zone of low attenuation due to hemorrhage surrounding the pulmonary nodule was reported in only one patient, and none of the patients had the air crescent sign, which represents a crescent-shaped lucency in the region of the original nodule secondary to necrosis. The lack of these characteristic signs in the COPD patients is not surprising, since these signs were mainly described in neutropenic patients with IPA.[48,49]

The value of bronchoscopy and BAL in the diagnosis of IPA has been studied extensively. However, these studies were mainly in immunocompromised patients. The overall positive diagnostic yield was around 50%, with some studies showing lower diagnostic yield (less than 30%).[50–52] There are limited reports on the role of transbronchial biopsies in the diagnosis of IPA that show that this intervention did not add much to the yield of BAL with increased risk of complications.[50] There are no studies on the value of bronchoscopy in the diagnosis of IPA in COPD patients. In this analysis, BAL was positive in 70% of those patients in whom the procedure was done. Transbronchial biopsy was reportedly done in six patients, and was positive for *Aspergillus* invading the lung parenchyma in all of these patients. It appears that BAL with or without transbronchial biopsies may be a useful test in COPD patients with high clinical or radiological suspicion of IPA or not responding to conventional antibiotics.

Twenty percent of patients had other respiratory pathogens at the same time. There are some reports that suggest that their may be concomitant infections with IPA. Some studies even reported IPA following influenza infection.[53,54] The finding of a concomitant respiratory infection further complicates the diagnosis of IPA in these patients in whom a pathogen was isolated. If there is atypical radiological pattern or the patient does not respond appropriately to antibiotics, then unusual infections such as IPA need to be considered.

The most recent advances in the diagnosis of IPA are related to detecting *Aspergillus* antigens (such as galactomannan, PCR and $(1 \rightarrow 3)$-β-D-glucan) in body fluids.[55,56] Elevated Serum galactomannan was reported in only one COPD patient with IPA. The majority of the cases in this analysis were reported prior to the routine use of this assay in patients suspected to have IPA. Galactomannan is a polysaccharide cell-wall component that is released by *Aspergillus* during growth. A double sandwich ELISA for the detection of galactomannan in the serum is the best characterized test, and was recently approved by the Food and Drug Administration for the diagnosis of IPA. It is reported that serum galactomannan can be detected several days before the presence of clinical signs, an abnormal chest radiograph or positive culture. Thus, galactomannan detection may allow earlier confirmation of the diagnosis and serial determination of serum galactomannan values may be useful in assessing the evolution of the infection during treatment. Overall the galactomannan assay has a sensitivity of 71 and specificity of 89% for proven cases of invasive aspergillosis. Its negative predictive value is 92–98% and the positive predictive value is between 25 and 62%.[57] There is evidence that galactomannan is detected in other body fluids such as BAL, urine and cerebrospinal fluid, and that these tests may become positive prior to clinical and radiological findings suggestive of IPA.[58–61] Polymerase chain reaction is another way to diagnose IPA by the detection of *Aspergillus* DNA in BAL fluid and serum. A positive

Aspergillus PCR in BAL fluid has an estimated sensitivity of 67–100% and specificity between 55 and 95%.[62] Polymerase chain reaction sensitivity and specificity have also been reported as 100 and 65–92%, respectively in serum samples.[62–65] However, this test is often associated with false positive results because it does not discriminate between colonization and infection. Polymerase chain reaction for *Aspergillus* DNA detection remains restricted to highly specialized laboratories and cannot be considered as a routine exam.

The role of galactomannan and other serological studies in the diagnosis of IPA is evolving. Furthermore, their role in different hosts such as patients with COPD, as surveillance tools, and their impact on the outcome of patients are not clear. Until solid data are available, these tests should be considered as adjunct diagnostic studies, and should not replace appropriate clinical and radiological evaluation, and in selected cases, invasive procedures to confirm the diagnosis of IPA.

The majority of patients in this report were treated by amphotericin B, and some patients were treated by itraconazole. This is primarily because almost all the reviewed reports were prior to the introduction of the newer, and more effective anti-fungal agents. It is known that amphotericin B and itraconazole are not very effective in the treatment of severe IPA, and in the case of Amphotericin B is associated with significant side effects that limit its tolerance and continuation of therapy. This is especially important in this patient population who tend to be older patients with multiple medical problems including renal disease that may limit their tolerance to Amphotericin B. Lipid formulations of Amphotericin B are better tolerated and may be an alternative to conventional amphotericin B. Voriconazole is a new broad-spectrum triazole, which is approved as the initial treatment of invasive aspergillosis, and is currently considered the treatment of choice in many patients with IPA.[29,66,67] In a large prospective, randomized, multicenter trial, voriconazole was compared with amphotericin B as the primary therapy for IPA in immunocompromised patients.[68] Those patients receiving voriconazole had a higher favorable response rate at week 12 (53 compared with 32% in patients receiving amphotericin B) and a higher 12-week survival (71 compared with 58%). Voriconazole is available in both intravenous and oral formulations and has a milder side effect profile, and is much better tolerated than amphotericin B. There is only one documented case, in this report, of treatment with voriconazole in a COPD patient with IPA. Posaconazole and Echinocandin derivatives such as caspofungin, micafungin and anidulafungin are other agents that can be used in the treatment of IPA refractory to standard treatment or if the patient could not tolerate first line agents.[69,70]

The mortality of COPD patients with IPA described in this report exceeded 90% and is higher than that reported for other severely immunocompromised patients. The overall mortality of IPA in patients with classic risk factors for IPA such as neutropenia, hematological malignancy and hematopoietic stem cell transplantation has improved in the last few years and is in the range of 40–90%.[71,72] We believe the main reason for this exceedingly high mortality in COPD patients is related to delay in the diagnosis of IPA, since it is not routinely thought of in this patient population. It has been shown that maintaining high index of suspicion and early diagnosis of IPA is associated with improved outcome.[73] Other potential factors associated with high mortality of IPA in COPD patients are older age, poor pulmonary reserve and multiple comorbid illnesses. Obviously, the retrospective analysis of the published literature may be associated with selection bias that may contribute to this high mortality rate. The outcome of IPA in COPD patients would probably improve by increased awareness of this serious infection in this patient population, especially those with severe COPD and/or on chronic corticosteroids therapy. Other interventions that may improve survival are the early use of HRCT of the chest in patients suspected to have IPA and the introduction of noninvasive diagnostic methods such as detecting *Aspergillus* antigens by galactomannan or PCR. Furthermore, more effective and better tolerated anti-fungal agents such as triazoles and echinocandins may improve the outcome of these patients.

In conclusion, IPA is increasingly recognized infection in patients with COPD (Table 6). The reasons why these patients are at risk for this severe infection are not clear, however most of the patients appear to have severe underlying lung disease and are on chronic corticosteroid therapy. The clinical presentation of IPA

Table 6 Summary of key learning points related to IPA in patients with COPD

Chronic obstructive pulmonary disease is increasingly recognized as a risk factor for IPA
Severe lung disease and/ or chronic corticosteroid therapy appear to be the main risk factors for IPA in patients with COPD
The clinical and radiological presentation of IPA in patients with COPD is nonspecific and high index of suspicion is warranted
Isolation of *Aspergillus* spp. from lower respiratory tract specimen in patients with COPD should not be routinely dismissed as colonization
Appropriate work up of COPD patients suspected to have IPA may include HRCT of the chest, bronchoscopy and possibly biopsy
Mortality in COPD patients with IPA is very high
Prospective multicenter trials are needed to better define the risk factors, diagnosis and outcome of IPA in patients with COPD

in this patient population is non specific and high index of suspicion is warranted to avoid delay in the diagnosis and management of these patients. Prospective multicenter trials are needed to define the risk factors of IPA in patients with COPD and to determine the role of the different diagnostic methods, including bronchoscopy and serology in the diagnosis of IPA in these patients.

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